Towards Organometallic Antischistosomal Drug Candidates

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Towards Organometallic Antischistosomal Drug Candidates

Key Terms

Organometallic complexes: Organometallic complexes are metal-based compounds, which have at least a direct bond between a metal centre and a carbon atom.[1] The most representative examples of this class of compounds are metallocenes, metal-arenes or metal-carbonyl complexes.[1]

Ferrocene: Ferrocene is an organometallic compound, which is characterized by two cyclopentadienyl rings sandwiching a Fe(II) atom. It is the most studied organometallic compound to date.[1]

Ferroquine: Ferroquine is a ferrocenyl derivative of the organic antimalarial drug chloroquine. In contrast to the parent organic drug, Ferroquine is also active on *P. falciparum* strains which are resistant to chloroquine.[2] Ferroquine is the most advanced organometallic-containing drug candidate.

Abstract

In the recent years, there has been an increasing interest in the use of novel approaches for the treatment of parasitic diseases such as schistosomiasis. Among the different approaches used, organometallic compounds were found to offer unique opportunities in the design of antiparasitic drug candidates. A ferrocenyl derivative, namely ferroquine, has even entered clinical trials as a novel antimalarial. In this short review, we report on the studies describing the use of organometallic compounds against schistosomiasis.

Background

In the developing world, particularly in tropical and subtropical regions of sub-Saharan Africa, Asia and America, parasitic helminth infections are a major human health problem affecting more than 1.5 billion people.[3] Of these infections, schistosomiasis, a neglected tropical disease (NTD) also named bilharzia, is one of the most prevailing parasitic diseases. It is caused by a genus of trematodes, schistosomes, which are dioecious blood flukes with a complex life cycle.[3] *Schistosoma haematobium*, *S. mansoni*, *S. intercalatum*, *S. japonicum* and *S. mekongi* are the five species responsible for human infections leading either to intestinal or urogenital schistosomiasis.[4] Each year, 11,700 deaths are reported, though the real figure might be as high as 280,000, which are related to the severe consequences of the infection such as fibrosis, renal failure or bladder cancer.[5-7] Even more worrying are the number of people infected worldwide (more than 207 million) and the number of people at risk of being infected (almost 800 million people), and this is among the world`s poorest populations.[8] In contrast to classical “first world diseases” and the so called big three diseases (malaria, tuberculosis and HIV/Aids), NTDs have attracted much lower research interests. This fact is easily reflected in the lack of new chemical entities (NCE) introduced into the market between 1999 and 2011 for NTDs.[9] Not only the number of available and approved drugs for NTDs is limited but also their development is lacking. This can be seen in the number of registered clinical trials in the period 1999-2011 focusing on NTDs: only 2016 out of 148 000 registrations are linked to

NTDs (about 1%).[10, 11] As a matter of fact, since the market launch of praziquantel (PZQ), which is the only available drug since the 1970s to treat all classes of schistosomiasis, no new drug has entered the market.[12] Please note that the chemotherapeutic treatment of schistosomiasis gradually increased from 12.4 million people in 2006 to over 42.1 million people treated in 2012 and is expected to increase further.[13, 14]

The past decade has seen the rapid development of organometallic compounds, which are metal complexes containing at least one direct metal-carbon bond, in various fields such as medicinal chemistry and chemical biology.[1, 15-22] Traditionally, organometallic compounds are noted to be relatively lipophilic, regularly uncharged and the metal centre is in a low oxidation state, making them attractive for biological purposes.[1] Indeed, organometallic compounds notably ferrocenyl derivatives[23, 24] have shown over the recent years promising anticancer[25], antibacterial[26] and antimalarial[27] properties. The advantages of organometallic derivatization of known organic drugs such as the antimalarial drug chloroquine (ferroquine) or the anticancer agent tamoxifen (ferrocifen) have been exemplified in the pioneering work of Biot,[27] Jaouen and co-workers.[28] In both examples, the incorporation of a ferrocenyl moiety into the organic drug allowed new and unique metal-specific modes of action to be unveiled in addition to superior activities compared to the parent drugs.

In this short review article, we highlight, on the basis of selected literature examples, the recent achievements on the design of organometallic drug candidates as antischistosomal agents. We especially focus our attention on the advantages provided by the addition of an organometallic moiety into a drug candidate. Of note, we are describing only the reports on organometallic compounds. Those related to classical coordination metal complexes are intentionally omitted. The organometallic compounds presented in this short review are categorized into three main groups according to the nature of the parent organic drug and their metal derivatization (antifungal agents as antischistosomal drug candidates, antimalarial agents as antischistosomal drug candidates and organometallic derivatives of PZQ). Their *in vitro* and/or

in vivo antischistosomal activity, cytotoxicity and stability, when possible, are discussed in detail.

Antifungal agents as antischistosomal drug candidates

Over the recent years, metal-drug synergism was shown to hold great promise for the development of antiparasitic drug candidates.[29, 30] This approach makes use of the combination of a biologically active drug and a metal fragment to further enhance the biological activity of the parent molecule.[29] For example, the application of such a strategy was previously investigated by the group of Sanchez-Delgado, who prepared organoruthenium complexes bearing the azoles antifungal agents clotrimazole and ketoconazole as coordinating ligands and investigated their antiparasitic effect against *Leishmania major* (causing leishmaniasis) and *Trypanosoma cruzi* (the causative agent of Chagas disease).[29, 31] Complexation of clotrimazole to a ruthenium complex increased the activity of the organic drug against *L. major* and *T. cruzi* by a factor of 110 and 58, respectively, while no toxicity to human osteoblast was observed.

In the field of antischistosomal drug candidates, a series of miconazole (**mcz**) organoruthenium complexes with the general formula [(η^6-p-cymene)$RuCl_2$(mcz)], [(η^6-p-cymene)$RuCl(mcz)_2$]Cl and [(η^6-p-cymene)$Ru(mcz)_3$]$(PF_6)_2$ were synthesized by Turel *et al*. as potential antifungal and antischistosomal agents (Figure 1).[32]

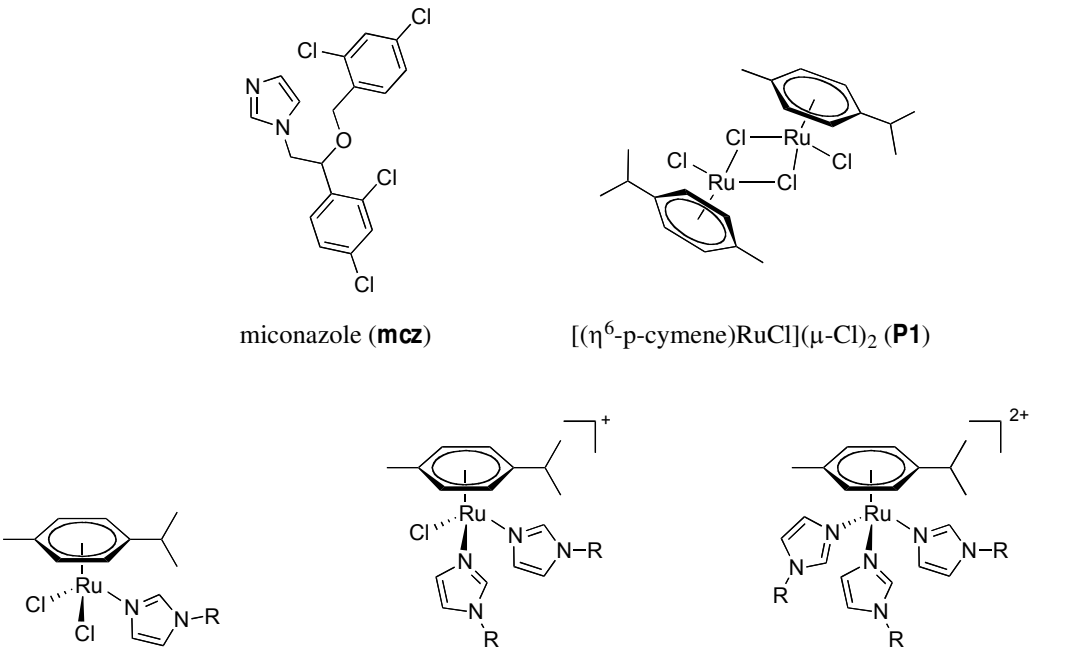

Figure 1. Structures of the antifungal miconazole (mcz), the dimeric ruthenium precursor (P1) and the general formulas of the mono-, bis-, and tris-azole organoruthenium species. The azole ligands are abbreviated and linked *via* the N3 imidazole nitrogen atom of miconazole. Figure adapted from ref.[32]

In their study, the authors used the dimeric ruthenium precursor [(η^6-*p*-cymene)RuCl]$_2$(μ-Cl)$_2$ (**P1**) as a reference compound and compared its activity to the respective *mono*-, *bis*- and *tris*-azole organoruthenium species prepared. No effect was observed when **P1** was incubated with adult *S. mansoni* for 72 h at a concentration of 100 μg/mL. In contrast, the mcz complexes ([(η^6-p-cymene)RuCl$_2$(mcz)], [(η^6-p-cymene)RuCl(mcz)$_2$]Cl and [(η^6-p-cymene)Ru(mcz)$_3$](PF$_6$)$_2$) had an increasing activity at 100 μg/mL after 24–48 h post-incubation with decreasing numbers of mcz ligands ([(η^6-p-cymene)RuCl$_2$(mcz)] > [(η^6-p-cymene)RuCl(mcz)$_2$]Cl > [(η^6-p-cymene)Ru(mcz)$_3$](PF$_6$)$_2$). Interestingly, [(η^6-p-cymene)Ru(mcz)$_3$](PF$_6$)$_2$ showed a sex-specific *in vitro* activity. After 72 h incubation of [(η^6-p-cymene)Ru(mcz)$_3$](PF$_6$)$_2$, all male worms died, while female worms showed decreased mortality.[32] Of note, a slow decomposition of the monoazole complex in DMSO, which was the solvent used in the bioassay, was observed. Such behaviour was also observed with other similar antiparasitical and

anticancer organometallic candidates.[33] Therefore, the *in vitro* results obtained for compound [(η^6-p-cymene)$RuCl_2$(mcz)] are a combination of the activity of mcz, compound [(η^6-p-cymene)$RuCl_2$(mcz)] and of [(η^6-p-cymene)$RuCl_2$(DMSO)]. However, as nicely described by the authors, no decomposition of the di- and tri-substituted complexes was observed in DMSO.

Antimalarial agents as antischistosomal drug candidates

Drug-repurposing has become an important tool over the past years for the discovery and development of new medicines. This strategy, particularly for neglected diseases where research is mostly academically driven, can allow saving an enormous amount of time, money and effort.[34] Technically speaking, the aim is to use an already known and/or approved drug to treat a (completely) different disease.[35] In the case of schistosomiasis, whose treatment relies on a single drug (PZQ), new perspectives are urgently needed to supply the drug development pipeline with new lead compounds. Therefore, this strategy might hold great promise.[35] Besides the economical perspective, another advantage might be the ability to treat two diseases simultaneously. For example, since helminth infections and malaria are often coendemic, treatment with an antimalarial drug in patients suffering from a *Plasmodium*/schistosome co-infection might show an ancillary effect on schistosomiasis.[36] Since both blood-feeding parasites, *Plasmodium* and *Schistosoma*, share the heme degradation pathway, drug candidates might interact with similar targets.[37] With this in mind, our groups in collaboration with the one of Biot used this approach and analysed the potential of the organometallic antimalarial drug candidates ferroquine, ruthenoquine and hydroxyl-ferroquine (Figure 2) as antischistosomal agents.[38-40] For comparison, the known antimalarial drugs chloroquine and mefloquine were used as reference compounds. Of note, the latter is known for its antischistosomal effects.[41] Ruthenoquine and hydroxyl-ferroquine were employed in this study to assess if redox-activity and/or production of reactive oxygen species (ROS) could be playing a role in the potential biological

activity. Indeed, contrary to ferroquine, ruthenoquine cannot be oxidized under physiological conditions while hydroxyl-ferroquine can produce hydroxyl radicals like ferroquine but has reduced cytotoxic effects.[42]

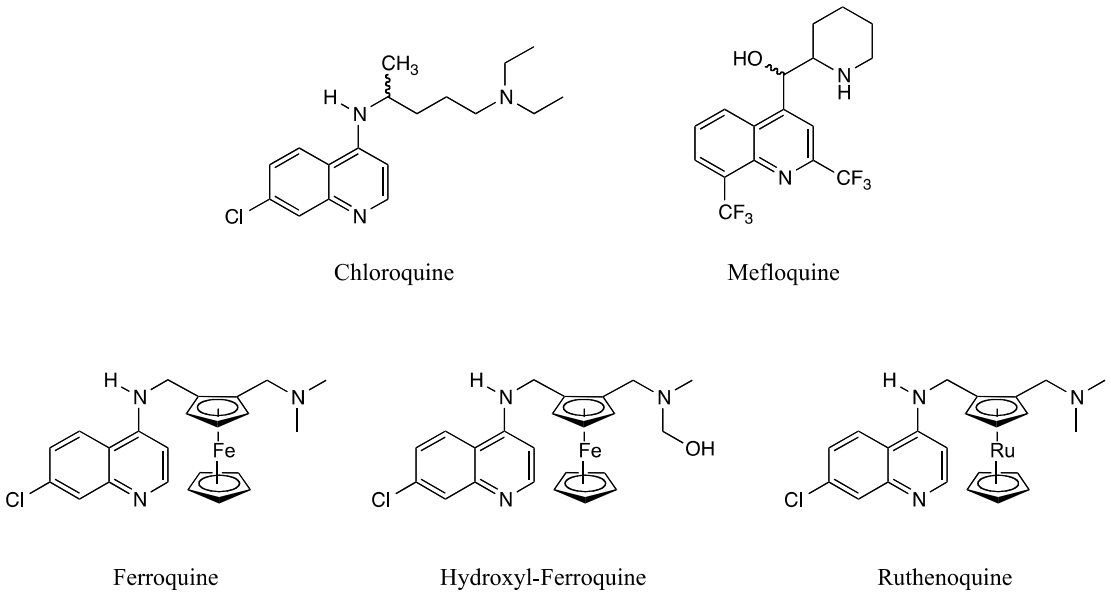

Figure 2. Chemical structures of chloroquine, mefloquine, ferroquine, hydroxyl-ferroquine and ruthenoquine. Figure adapted from ref.[38]

The cytotoxicity of all compounds was first evaluated on both cervical cancer cells (HeLa) and non-cancerous cells (MRC-5) to ensure that the compounds were selective towards parasites over cells. Mefloquine was shown to be the most toxic, while the other organometallic compounds showed moderate toxicity. Among the organometallic derivatives, ruthenoquine displayed the lowest toxicity (IC_{50} values of 21.9 µM and 8.8 µM on MRC-5 and HeLa cell lines, respectively), while both ferrocenyl derivatives (ferroquine and hydroxyl-ferroquine) indicated cytotoxicities in a similar range[43]. The antischistosomal activity of the compounds was then assessed on newly transformed schistosomula (NTS) and adult *S. mansoni* both *in vitro* and *in vivo*. The *in vitro* results of all organometallic derivatives revealed a moderate antischistosomal activity against both NTS and adult *S. mansoni.* Within all organometallic compounds tested, ruthenoquine, which does not produce reactive oxygen species, was found to be the most effective. 72 h post-incubation with 33 µM of ruthenoquine, all NTS were dead whereas NTS

treated with ferroquine and hydroxyl-ferroquine showed reduced viability. The same trend was observed on adult *S. mansoni*. Exposure to ruthenoquine led to the strongest reduction in viability, and several dead worms were observed 72 h after post-incubation. *In vivo* studies revealed only weak antischistosomal activity of the organometallic compounds with the highest total worm burden reduction for ferroquine (19.4% and 35.6% when treated with 200 and 800 mg/kg, respectively). An even lower total worm burden reduction of 17.3% at 200 mg/kg was observed for hydroxyl-ferroquine, while ruthenoquine indicated no activity at this dosage. These observations show that *in vitro* results cannot always be translated into *in vivo* results. Of note, no antischistosomal activity was observed for chloroquine both *in vitro* and *in vivo*.[38] The results obtained suggest that ferrocenyl and ruthenocenyl derivatization of the antimalarial drug chloroquine is not significantly improving its antischistosomal activity.

Organometallic derivatives of praziquantel

As mentioned above, PZQ is the only available drug available against schistosomiasis.[8, 44] Apart from its broad-spectrum of activity, there are two main drawbacks associated with the use of PZQ, namely its inactivity against juvenile *Schistosoma* and its rather low metabolic stability *in vivo*.[45-47] Indeed, hydroxylation at the cyclohexane ring leads to the major metabolite (PZQ-OH), which lacks the activity of the parent drug (Figure 3).

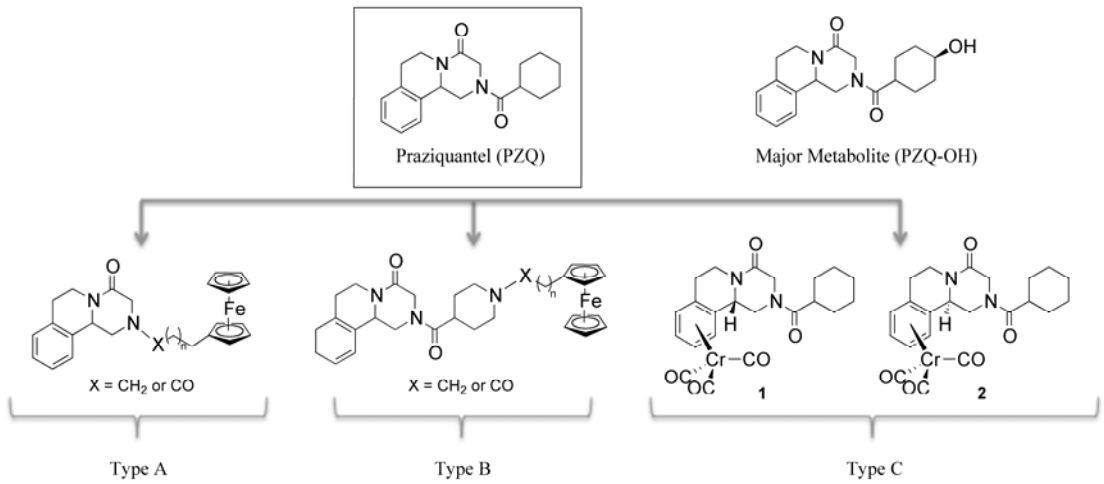

Figure 3. General structures of praziquantel (PZQ), the major metabolite (PZQ-OH) and the three classes of different organometallic derivatizaton (Type -A, -B and –C). Figure adapted from ref.[48]

With millions of people treated for schistosomiasis with a single drug, not very surprisingly, a reduced susceptibility of schistosomes to PZQ was recently reported in the literature.[49-51] This encouraged us to actively engage in this research field and hence two years ago we started a program on organometallic modifications of PZQ. Initially, 18 ferrocenyl derivatives of PZQ were synthesized, which are divided into two structural classes (Type A & Type B).[52] Type-A class of compounds lacks the cyclohexane ring of PZQ, which might avoid the transformation to a hydroxylated metabolite with reduced activity. Instead, the ferrocenyl moiety is attached to the praziquanamine by various linkers. The second class of compounds (Type-B) bears a piperidine instead of a cyclohexane ring where the ferrocenyl moiety is attached. Previous studies on the parent drug suggest that such modifications should not reduce the anthelmintic activity.[53, 54]

More specifically, we could demonstrate a high stability of the compounds in human plasma using a LC-MS technique.[55] This observation contradicts the common thinking that some organometallic compounds could be unstable in a biological environment. The cytotoxicity against two mammalian cell lines (HeLa and MRC-5) was then evaluated to ensure the selectivity of the compounds. The resulting 18 organometallic derivatives achieved only

moderate cytotoxicities toward HeLa cell (IC_{50} values in a range of 16.9 – 97.7 μM) and did not strongly affect healthy MRC-5 cell. Interestingly, most of the ferrocenyl derivatives, with the exception of one diferrocenyl type-B compound (X = CO, n = 2), showed a strong decrease in their cytotoxicity on a noncancerous cell line (MRC-5) compared to HeLa cells.

Finally, the *in vitro* antischistosomal activity against adult *S. mansoni* was evaluated. Out of the 18 ferrocenyl derivatives, only 4 compounds, which all belong to the type-A class, showed antischistosomal activity at 30 μg/mL *in vitro*. Since only a moderate antischistosomal activity was observed for these eighteen ferrocenyl derivatives of PZQ, a different organometallic modification was envisaged. Hence, the aromatic part of PZQ was complexed with a $Cr(CO)_3$ core (Type C). It was hypothesized that this organometallic fragment might decrease the metabolic instability of PZQ and improve the general physicochemical properties of the parent drug by increasing for example its lipophilicity.[48] The evaluated lipophilicities, given as the logarithmic distribution coefficient (D) at physiological conditions (pH =7.4), of both compounds **1** ($LogD_{7.4}$ = 3.49) and **2** ($LogD_{7.4}$ = 3.59) were significantly higher than that of PZQ ($LogD_{7.4}$ = 2.66) and were attributed to the presence of the $Cr(CO)_3$ moiety. The membrane permeability or **1** and **2** was therefore assumed to be increased compared to PZQ. The *in vitro* studies of the Cr-PZQ derivatives against adult *S. mansoni* revealed an impressive submicromolar antischistosomal activity of **1** (0.25 μM) and **2** (0.27 μM), with a biological effect in a comparable range than the parent drug PZQ (0.1 μM). Importantly, **1** and **2** were found to be mainly non toxic on the cervical cancer (HeLa) and non-cancerous (MRC-5) cell lines, showing therefore a promising selectivity for parasites.[48]

The stability of both Cr-PZQ derivatives were preliminary investigated by ^1H Nuclear Magnetic Resonance (NMR) spectroscopy to ensure that the anthelmintic activity is not due to a release of the organometallic $Cr(CO)_3$ core. The compounds were found to be stable up to two days in a $[D_6]DMSO/D_2O$ mixture. These findings were further supported with human plasma stability

experiments, which showed no significant decomposition after incubation for 24 hours at 37 °C.

Further bioassays were undertaken to study in-depth the *in vitro* metabolic behaviour of both chromium compounds using human liver microsomes.[56] In general, the metabolic profile obtained for **1** and **2** shows crucial differences. While **1** is mainly demetallated to PZQ or hydroxylated to *cis*-4-PZQ-OH, **2** shows only minor demetallation and hydroxylation. The major metabolite of **2** could be identified as [(η^6-praziquanamine)$Cr(CO)_3$], formed after cleavage of the cyclohexanoyl moiety. The detailed metabolic profiles of **1** and **2** are shown in Figure 4.[56]

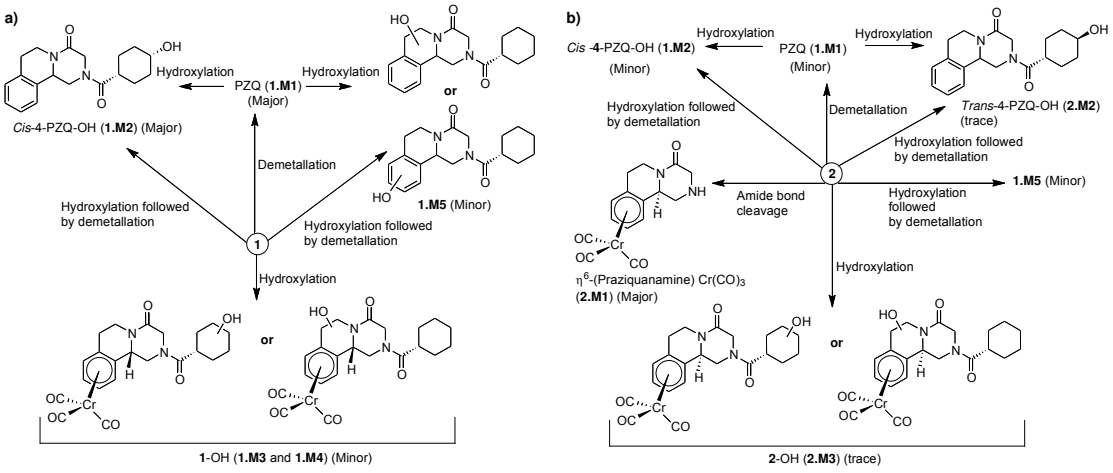

Figure 4. Metabolic profile of 1 and 2 suggested by Gasser and co-workers. For compounds 1 and 2, see Figure 3. Figure taken from ref.[56]

At this stage, it is necessary to clarify that only one of the enantiomers of the parent drug PZQ ((*R*)-PZQ) exhibits an antischistosomal activity *in vitro.* Also, (*R*)-PZQ is believed to have fewer adverse events than the (*S*)-PZQ enantiomer.[57] Consequently, optically pure (η^6-PZQ)$Cr(CO)_3$ derivatives, namely (R,R_P)-**1**, (S,S_P)-**1**, (S,R_P)-**2** and (R,S_P)-**2** were synthesized and investigated for their *in vitro* antischistosomal activity against adult *S. mansoni* (Figure 5).

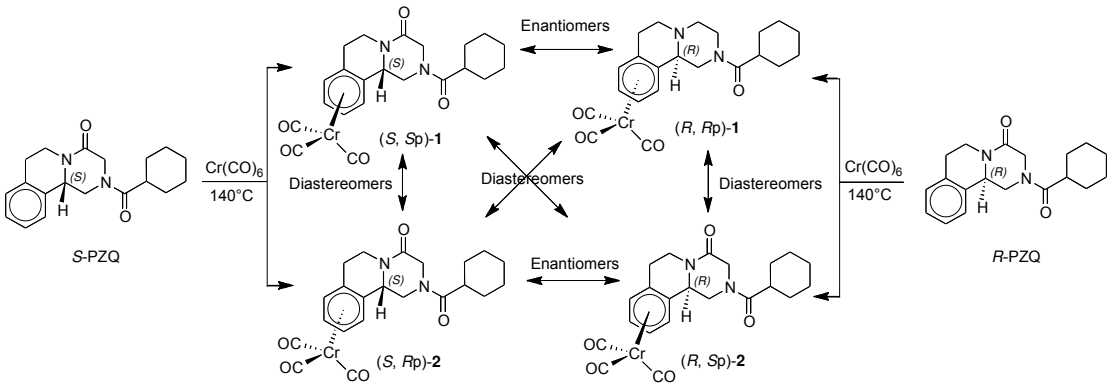

Figure 5. **Synthesis of optically pure (η^6-PZQ)$Cr(CO)_3$ derivatives starting from *S*-PZQ and *R*-PZQ. Figure taken from ref.[56]**

A clear difference in activity was observed, with the lowest IC_{50} value for (R,R_P)-**1** of 0.08 μM, followed by (R,S_P)-**2** with 0.13 μM. The (*S*)-enantiomers ((S,S_P)-**1**, (S,R_P)-**2**) exhibited IC_{50} values higher than 66.9 μM and are therefore considered as inactive (see Table 1).

Table 1. ***In vitro*** **antischistosomal activity against adult S. mansoni of enantiomeric mixtures of compounds 1 and 2, PZQ and optically pure derivatives. Table taken from ref.[56]**

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
PZQ	0.10		
1[a]	0.25	(R,R_P)-**1**	0.08
		(S,S_P)-**1**	>66.9
2[a]	0.27	(R,S_P)-**2**	0.13
		(S,R_P)-**2**	>66.9

[a] Racemic mixture.

These observations tend to suggest that the (*R*)-enantiomers of (η^6-PZQ)$Cr(CO)_3$ have the same target as PZQ. *Rac*-**1** and *Rac*-**2** were then given to mice harbouring adult *S. mansoni* to evaluate their *in vivo* antischistosomal activity. Relatively low total worm burden reduction of 24% and 29%, respectively were obtained with single doses of 400 mg/kg of **1** and

2. Of note, with the same dosage of 400 mg/kg, PZQ reached a total worm burden reduction of 96%.[58] Distribution problems or protein binding might explain these relatively disappointing *in vivo* results[56]. Of note, death of mice was observed during this *in vivo* study. Contrary to expectations, it is very important to mention that a release of the $Cr(CO)_3$ core cannot be responsible for the observed toxicities. Assuming that all chromium given to mice was transformed into Cr(III) (note that this transformation involves the passage through other oxidation states), the amount of Cr(III) would not be sufficient to kill mice since Cr(III) salts have LD_{50} values in the range 3.2 – 15 g/kg when given orally to mice.[56, 59] Taken together, the toxicity observed in mice during the *in vivo* studies may be rationalized with the parasitic infection itself and is most likely not related with the administration of the chromium compounds.

Future perspectives

There is undoubtedly a need for novel antischistosomal drug candidates. To tackle this global problem, it is extremely important that different perspectives are employed to enlarge as soon as possible the pool of compounds to be tested. Therefore, the use of organometallic compounds as antischistosomal agents is definitively not an idea to be put aside. Considering the extremely low amount of literature on this topic (to the best of our knowledge, there are only 5 publications reported on this subject to date) and the relatively promising results obtained, we strongly believe that much more efforts should be put into this research area. Organometallic compounds clearly offer new and unique opportunities. In addition, potentially, novel metal-mediated modes of action could be unveiled. We are currently assessing the activity of novel organometallic derivatives and our results will be published in due course.

Executive summary

Background

- Schistosomiasis is a parasitic helminth infection, which belongs to the neglected tropical disease (NTD).
- More than 200 million people are infected with schistosomes and over 800 million people are at risk.
- Current treatment options rely on praziquantel.
- This review discusses the potential of the synthetic modification of known antischistosomal agents with organometallic compounds to provide new lead compounds against schistosomiasis.

Antifungal agents as antischistosomal drug candidates

- Metal-drug synergism is exemplified with the biological evaluation of a series of miconazole (mcz) organoruthenium complexes as antischistosomal agents.
- The *in vitro* antischistosomal results for three different complexes, namely [(η^6-p-cymene)$RuCl_2$(mcz)], [(η^6-p-cymene)RuCl(mcz)$_2$]Cl and [(η^6-p-cymene)Ru(mcz)$_3$]$(PF_6)_2$, are discussed and compared to a dimeric ruthenium precursor.
- A sex-specific *in vitro* activity for [(η^6-p-cymene)Ru(mcz)$_3$]$(PF_6)_2$ was observed.

Antimalarial agents as antischistosomal drug candidates

- Drug-repurposing has become an interesting tool for the cost-effective development of new drugs. Not surprisingly, researchers have tried to find new lead compounds as antischistosomal drugs using this technique.

- The *in vitro* and *in vivo* antischistosomal effect of organometallic antimalarial drug candidates such as ferroquine, ruthenoquine and hydroxyl-ferroquine is discussed in depth in this section.

Organometallic derivatives of praziquantel

- The widespread possibilities of organometallic derivatization of a known organic antischistosomal drug such as praziquantel is described in this part of the review.
- The *in vitro* antischistosomal activity of eighteen ferrocenly derivatives of PZQ, which belong to two different structural classes, is discussed.
- *In vitro* and *in vivo* studies on two organometallic modified PZQ at the aromatic part with a $Cr(CO)_3$ core are presented.
- The *in vitro* metabolic behaviour of two chromium compounds is highlighted.

* [52]: Patra M, Ingram K, Pierroz V *et al.*: Ferrocenyl Derivatives of the Anthelmintic Praziquantel: Design, Synthesis, and Biological Evaluation. *J. Med. Chem* 55(20), 8790-8798 (2012).

- This article present the first ferrocenyl modified praziquantel derivatives as well as their *in vitro* antischistosomal activity.

* [48]: Patra M, Ingram K, Pierroz V *et al.*: [(η6-Praziquantel)Cr(CO)3] Derivatives with Remarkable In Vitro Anti-schistosomal Activity. *Chem. Eur. J.* 19(7), 2232-2235 (2013).

- This article shows the impressive *in vitro* antischistosomal activity of two chromium compounds.

* [56]: Patra M, Ingram K, Leonidova A *et al.*: In Vitro Metabolic Profile and in Vivo Antischistosomal Activity Studies of (n6-Praziquantel)Cr(CO)3 Derivatives. *J. Med. Chem* 56(22), 9192-9198 (2013).

- This article presents an in-depth biological study of $Cr(CO)_3$(PZQ).

* [38]: Keiser J, Vargas M, Rubbiani R, Gasser G, Biot C: In vitro and in vivo antischistosomal activity of ferroquine derivatives. Parasites & Vectors 7(1), 424 (2014).

- This article presents an exemplified drug-repurposing study of known organometallic antimalarial drug candidates as antischistosomal agents.

* [32]: Kljun J, Scott AJ, Lanisnik Rizner T, Keiser J, Turel I: Synthesis and Biological Evaluation of Organoruthenium Complexes with Azole Antifungal Agents. First Crystal Structure of a Tioconazole Metal Complex. *Organometallics* 33(7), 1594-1601 (2014).

- This article show drug-synergism adapted for an antifungal organoruthenium complex and translated it for antischistosomal purposes.

* [2]: Biot C, Glorian G, Maciejewski LA, Brocard J: Synthesis and antimalarial activity in vitro and in vivo of a new ferrocene−chloroquine analogue. *J. Med. Chem.* 40, 3715-3718 (1997).

- This is the seminal article on Ferroquine, the ferrocenyl analogue of chloroquine, which went into phase II clinical trial.

* [28]: Hillard EA, Vessieres A, Jaouen G: *Ferrocene Functionalized Endocrine Modulators as Anticancer Agents*. In: *Medicinal Organometallic Chemistry (Topics in Organometallic Chemistry)*, Jaouen G, Metzler-Nolte N (Ed.^(Eds). Springer, Heidelberg, Germany 81-117 (2010).

- This book chapter presents the recent advences on Ferroquine, the ferrocenyl analogue of the anticancer drug Tamoxifen.

*[11]: Njoroge M, Njuguna NM, Mutai P, Ongarora DSB, Smith PW, Chibale K: Recent Approaches to Chemical Discovery and Development Against Malaria and the Neglected Tropical Diseases Human African Trypanosomiasis and Schistosomiasis. *Chem. Rev.* 114(22), 11138-11163 (2014).

- This review highlights the recent approches to chemical discovery for neglected tropical diseases such as schistosomiasis.

References

1. Gasser G, Ott I, Metzler-Nolte N: Organometallic Anticancer Compounds. *J. Med. Chem* 54(1), 3-25 (2011).
2. Biot C, Glorian G, Maciejewski LA, Brocard J: Synthesis and antimalarial activity in vitro and in vivo of a new ferrocene–chloroquine analogue. *J. Med. Chem.* 40, 3715-3718 (1997).
3. Lee EF, Young ND, Lim NTY, Gasser RB, Fairlie WD: Apoptosis in schistosomes: toward novel targets for the treatment of schistosomiasis. *Trends in Parasitology* 30(2), 75-84 (2014).
4. Colley DG, Bustinduy AL, Secor WE, King CH: Human schistosomiasis. *Lancet* 383(9936), 2253-2264 (2014).
5. Sayed AA, Simeonov A, Thomas CJ, Inglese J, Austin CP, Williams DL: Identification of oxadiazoles as new drug leads for the control of schistosomiasis. *Nat Med* 14(4), 407-412 (2008).
6. Liu R, Dong H-F, Guo Y, Zhao Q-P, Jiang M-S: Efficacy of praziquantel and artemisinin derivatives for the treatment and prevention of human schistosomiasis: a systematic review and meta-analysis. *Parasites & Vectors* 4(1), 201 (2011).
7. Hotez PJ, Fenwick A, Savioli L, Molyneux DH: Rescuing the bottom billion through control of neglected tropical diseases. *Lancet* 373(9674), 1570-1575 (2009).
8. Steinmann P, Keiser J, Bos R, Tanner M, Utzinger J: Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk. *Lancet Infect. Dis.* 6(7), 411-425 (2006).

9. Trouiller P, Olliaro P, Torreele E, Orbinski J, Laing R, Ford N: Drug development for neglected diseases: a deficient market and a public-health policy failure. *Lancet* 359(9324), 2188-2194 (2002).
10. Pedrique B, Strub-Wourgaft N, Some C *et al.*: The drug and vaccine landscape for neglected diseases (2000-11): a systematic assessment. *Lancet Global Health* 1(6), e371-e379 (2013).
11. Njoroge M, Njuguna NM, Mutai P, Ongarora DSB, Smith PW, Chibale K: Recent Approaches to Chemical Discovery and Development Against Malaria and the Neglected Tropical Diseases Human African Trypanosomiasis and Schistosomiasis. *Chem. Rev.* 114(22), 11138-11163 (2014).
12. Thétiot-Laurent SaL, Boissier J, Robert A, Meunier B: Schistosomiasis Chemotherapy. *Angew. Chem. Int. Ed.* 52(31), 7936-7956 (2013).
13. Who Fact Sheet No. 115 F, (Document available at http://www.who.int/mediacentre/factsheets/fs115/en// ; November 2014).
14. Rollinson D, Knopp S, Levitz S *et al.*: Time to set the agenda for schistosomiasis elimination. *Acta Tropica* 128(2), 423-440 (2013).
15. Hartinger CG, Metzler-Nolte N, Dyson PJ: Challenges and Opportunities in the Development of Organometallic Anticancer Drugs. *Organometallics* 31, 5677–5685 (2012).
16. Gasser G, Metzler-Nolte N: The Potential of Organometallic Complexes in Medicinal Chemistry. *Curr. Opin. Chem. Biol.* 16, 84-91 (2012).
17. Bruijnincx PC, Sadler PJ: New trends for metal complexes with anticancer activity. *Curr. Opin. Chem. Biol.* 12(2), 197-206; and references therein (2008).
18. Hartinger C, Dyson PJ: Bioorganometallic chemistry - from teaching paradigms to medicinal applications. *Chem. Soc. Rev.* 38, 391-401 (2009).
19. Jaouen G, Metzler-Nolte N: *Medicinal Organometallic Chemistry*. In: *Topics in Organometallic Chemistry*, (Ed.^(Eds). Springer, Heidelberg, Germany (2010).
20. Peacock AFA, Sadler PJ: Medicinal organometallic chemistry: designing metal arene complexes as anticancer agents. *Chem. Asian J.* 3(11), 1890-1899 (2008).
21. Patra M, Gasser G: Organometallic Compounds, an Opportunity for Chemical Biology. *ChemBioChem* 13, 1232 – 1252 (2012).
22. Gasser G: Inorganic Chemical Biology: Principles, Techniques and Applications. John Wiley & sons, Ltd, UK, (2014).
23. Salmain M, Metzler-Nolte N: *Bioorganometallic Chemistry of Ferrocene*. In: *Ferrocenes: Ligands, Materials and Biomolecules*, Stepnicka P (Ed.^(Eds). Wiley-VCH, Chichester 499-639 (2008).
24. Van Staveren DR, Metzler-Nolte N: The bioorganometallic chemistry of ferrocene. *Chem. Rev.* 104, 5931-5985, and references therein. (2004).
25. Gasser G, Ott I, Metzler-Nolte N: Organometallic Anticancer Compounds. *J. Med. Chem.* 54, 3-25 (2011).
26. Patra M, Gasser G, Metzler-Nolte N: Small organometallic compounds as antibacterial agents. *Dalton Trans.* 41, 6350-6358 (2012).

27. Dive D, Biot C: Ferrocene Conjugates of Chloroquine and other Antimalarials: the Development of Ferroquine, a New Antimalarial. *ChemMedChem* 3(3), 383-391 (2008).
28. Hillard EA, Vessieres A, Jaouen G: *Ferrocene Functionalized Endocrine Modulators as Anticancer Agents*. In: *Medicinal Organometallic Chemistry (Topics in Organometallic Chemistry)*, Jaouen G,Metzler-Nolte N (Ed.^(Eds). Springer, Heidelberg, Germany 81-117 (2010).
29. Martinez A, Carreon T, Iniguez E *et al.*: Searching for New Chemotherapies for Tropical Diseases: Ruthenium - Clotrimazole Complexes Display High in Vitro Activity against Leishmania major and Trypanosoma cruzi and Low Toxicity toward Normal Mammalian Cells. *J. Med. Chem* 55(8), 3867-3877 (2012).
30. Sanchez-Delgado RA, Anzellotti A: Metal Complexes as Chemotherapeutic Agents Against Tropical Diseases: Trypanosomiasis, Malaria and Leishmaniasis. *Mini Rev. Med. Chem.* 4(1), 23-30 (2004).
31. Iniguez E, Sanchez A, Vasquez M *et al.*: Metal-drug synergy: new ruthenium(II) complexes of ketoconazole are highly active against Leishmania major and Trypanosoma cruzi and nontoxic to human or murine normal cells. *J Biol Inorg Chem* 18(7), 779-790 (2013).
32. Kljun J, Scott AJ, Lanisnik Rizner T, Keiser J, Turel I: Synthesis and Biological Evaluation of Organoruthenium Complexes with Azole Antifungal Agents. First Crystal Structure of a Tioconazole Metal Complex. *Organometallics* 33(7), 1594-1601 (2014).
33. Patra M, Joshi T, Pierroz V *et al.*: DMSO-Mediated Ligand Dissociation: Renaissance for Biological Activity of N-Heterocyclic-[Ru(η6-arene)Cl2] Drug Candidates. *Chem. Eur. J.* 19(44), 14768-14772 (2013).
34. Abdulla M-H, Ruelas DS, Wolff B *et al.*: Drug Discovery for Schistosomiasis: Hit and Lead Compounds Identified in a Library of Known Drugs by Medium-Throughput Phenotypic Screening. *PLoS Negl Trop Dis* 3(7), e478 (2009).
35. Panic G, Duthaler U, Speich B, Keiser J: Repurposing drugs for the treatment and control of helminth infections. *International Journal for Parasitology: Drugs and Drug Resistance* 4(3), 185-200 (2014).
36. Hotez PJ, Brindley PJ, Bethony JM, King CH, Pearce EJ, Jacobson J: Helminth infections: the great neglected tropical diseases. *The Journal of Clinical Investigation* 118(4), 1311-1321 (2008).
37. Keiser J, Utzinger J: Antimalarials in the Treatment of Schistosomiasis. *Curr. Pharm. Des.* 18(24), 3531-3538 (2012).
38. Keiser J, Vargas M, Rubbiani R, Gasser G, Biot C: In vitro and in vivo antischistosomal activity of ferroquine derivatives. *Parasites & Vectors* 7(1), 424 (2014).
39. Navarro M, Castro W, Biot C: Bioorganometallic Compounds with Antimalarial Targets: Inhibiting Hemozoin Formation. *Organometallics* 31(16), 5715-5727 (2012).
40. Salas PF, Herrmann C, Orvig C: Metalloantimalarials. *Chem. Rev.* 113(5), 3450-3492 (2013).
41. Keiser J, Chollet J, Xiao S-H *et al.*: Mefloquine - An Aminoalcohol with Promising Antischistosomal Properties in Mice. *PLoS Negl Trop Dis* 3(1), e350 (2009).

42. Biot C, Daher W, Chavain N *et al.*: Design and Synthesis of Hydroxyferroquine Derivatives with Antimalarial and Antiviral Activities. *J Med Chem* 49(9), 2845-2849 (2006).
43. Jaouen G, Metzler-Nolte N: Topics in Organometallic Chemistry. Springer, 1, (2010).
44. Gryseels B: Schistosomiasis. *Infect. Dis. Clin. North Am.* 26(2), 383-397 (2012).
45. Cioli D, Pica-Mattoccia L, Archer S: Antischistosomal drugs: Past, present ... and future? *Pharmacology & Therapeutics* 68(1), 35-85 (1995).
46. Huang J, Bathena SPR, Alnouti Y: Metabolite Profiling of Praziquantel and its Analogs During the Analysis of in vitro Metabolic Stability Using Information-Dependent Acquisition on a Hybrid Triple Quadrupole Linear Ion Trap Mass Spectrometer. *Drug Metab. Pharmacokinet.* 25(5), 487-499 (2010).
47. Doenhoff MJ, Cioli D, Utzinger J: Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. *Curr. Opin. Infect. Dis.* 21, 659-667 (2008).
48. Patra M, Ingram K, Pierroz V *et al.*: [(η6-Praziquantel)Cr(CO)3] Derivatives with Remarkable In Vitro Anti-schistosomal Activity. *Chem. Eur. J.* 19(7), 2232-2235 (2013).
49. Ismail M, Botros S, Metwally A *et al.*: Resistance to praziquantel: direct evidance from *Schistosoma mansoni* isolated from Egyptian villegers. *Am. J. Trop. Med. Hyg.* 60, 932-935 (1999).
50. Melman SD, Steinauer ML, Cunningham C *et al.*: Reduced Susceptibility to Praziquantel among Naturally Occurring Kenyan Isolates of Schistosoma mansoni. *PLoS Negl. Trop. Dis.* 3(8), e504 (2009).
51. Greenberg RM: New approaches for understanding mechanisms of drug resistance in schistosomes. *Parasitology* 140(Special Issue 12), 1534-1546 (2013).
52. Patra M, Ingram K, Pierroz V *et al.*: Ferrocenyl Derivatives of the Anthelmintic Praziquantel: Design, Synthesis, and Biological Evaluation. *J. Med. Chem* 55(20), 8790-8798 (2012).
53. Ronketti F, Ramana AV, Chao-Ming X, Pica-Mattoccia L, Cioli D, Todd MH: Praziquantel derivatives I: Modification of the aromatic ring. *Bioorg. Med. Chem. Lett.* 17(15), 4154-4157 (2007).
54. Laurent SaL, Boissier J, Coslédan F, Gornitzka H, Robert A, Meunier B: Synthesis of "Trioxaquantel" Derivatives as Potential New Antischistosomal Drugs. *Eur. J. Inorg. Chem.* 2008(5), 895-913 (2008).
55. Lima RM, Ferreira MaD, Ponte TMDJ *et al.*: Enantioselective analysis of praziquantel and trans-4-hydroxypraziquantel in human plasma by chiral LC–MS/MS: Application to pharmacokinetics. *J. Chromatogr. B* 877, 3083-3088 (2009).
56. Patra M, Ingram K, Leonidova A *et al.*: In Vitro Metabolic Profile and in Vivo Antischistosomal Activity Studies of (n6-Praziquantel)Cr(CO)3 Derivatives. *J. Med. Chem* 56(22), 9192-9198 (2013).
57. Woelfle M, Seerden J-P, De Gooijer J, Pouwer K, Olliaro P, Todd MH: Resolution of Praziquantel. *PLoS Negl Trop Dis* 5(9), e1260 (2011).

58. Dong Y, Chollet J, Vargas M *et al.*: Praziquantel analogs with activity against juvenile *Schistosoma mansoni. Bioorg. Med. Chem. Lett.* 20, 2481-2484 (2010).
59. Levina A, Lay PA: Metal-based anti-diabetic drugs: advances and challenges*. Dalton Trans.* 40(44), 11675-11686 (2011).